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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,087	07/02/2001	Qingyun Liu	20330P	3793

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,087	LIU ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 5, 18-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Claims 1, 4, 5, 18-19 are pending and under consideration.

Response to Amendment and Arguments

The objection and rejections of claims 2-3 have been rendered moot by cancellation of the claims and are thus withdrawn.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5 stand rejected and new claims 18-19 are also rejected, under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility, for reasons of record set forth in the Office Action of 10/20/2003. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must

undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

It is clear from the instant specification that the nucleic acid encoding the HG52 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 18, line 11). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, even if, *arguendo*, the nucleic acid encoding the HG52 protein is found to be a G-protein coupled receptor, it is an orphan receptor. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of

record disclose any diseases or conditions associated with the function or expression of the HG52 protein, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. In the instant case, the fact that the claimed invention encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific ligand for each receptor is known, unless the biological activity of the receptor is disclosed and unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility.

The specification further asserts that the nucleic acid of the instant application can be used to treat certain diseases with compositions which modulates HG52 receptor signal activity, HG52 ligands, or levels of mRNA encoding HG52 (Specification at 17). However, this asserted utility is specific but not substantial. The specification does not disclose diseases associated with altered HG52 activity. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. There is no disclosure, for example, of whether the compounds could be administered orally or parentally, dosages, how to assay for improvement or intolerable levels of side effects, etc. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly

analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as HG52, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is known to be structurally analogous to proteins that are known in the art as G protein coupled receptors. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit its activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since

the instant specification does not disclose a "real world" use for HG52 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 1, 4-5 stand rejected and new claims 18-19 are also rejected, under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues that there is a specific, substantial and credible utility. This position is based on the observation that the teachings of the art of record clearly supports a finding that there was an art-recognized, well-established utility for thrombin-like receptors, exemplified by the disclosed polypeptide designated HG52. However, based upon the art recognized errors inherent in sequence-function methods of assigning protein function, and the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, and the fact that the change of a single amino acid can radically alter protein function, a nucleic acid encoding HG52 lacks a well-established, specific and substantial utility.

The Doerks reference was cited to show that it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors. Applicant argues that the Doerks reference addresses functional predictions based on sequence comparisons to unknown proteins. However, Doerks discuses several proteins which have had their function predicted based on homology to known proteins, for example, an assignment error was made for proteins gil2314657 and gil2688341 based on significant similarity to proline

dipeptidases, when this assignment was based on similarity of a region that was not the active site (page 248 column 3, third full paragraph)

Additionally, applicant cites Brenner et al. (PNAS USA 95 :6073-6078, 1998) as teaching that the most effective sequence searches are made by using statistical scores to interpret the results. Brenner et al. (1998) Proc. Natl. Acad. Sci. USA 95:6073-6078. Therein the authors, through exhaustive analysis of a dataset of proteins with known structural and functional relationships, determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues, and that 40% identity is a reliable threshold when aliened over at least 70 residue' s (pages 6073 and 6076.), and that the HG52 is 28.3% identical to PAR1L, a thrombin receptor. However, Yan et al. teaches that in certain cases, a change of even two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. Science 290: 523-527, 2000). Thus, the asserted utilities in the specification based upon the protein sequence homology are not specific and substantial.

Applicant further argues that orphan receptors have utility, citing Stadel. Applicant argues that use of the orphan GPCR's in selectivity screening is well recognized by those of skill in the art, and cites Stadel et al. to demonstrate this. However, Stadel et al. teaches that the initial challenge is to determine the function of each orphan receptor through the identification of activating ligands and, once the function is clarified, link the orphan receptor to a specific disease and thus establish it as a candidate for a comprehensive drug discovery effort (page 433, column 1, first paragraph). Thus Stadel et al. teaches that before an orphan GPCR has a use, the

activating ligand must be determined. Thus, without a known ligand, orphan receptors do not have a well-established, specific or substantial utility.

Applicant further argues that the encoded protein can be used for the identification of ligands. However, as discussed above, Stadel et al. teaches that before an orphan GPCR has a use, the activating ligand must be determined. Thus, without a known ligand, orphan receptors do not have a well-established, specific or substantial utility. This is only a research use and research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. See, e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." Moreover, such uses are not specific to the instant molecule, rather applicable to any nucleic acid molecules or proteins.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 31, 2004